Corneal Biomechanics: A Primer for Understanding Ectasia and CXL

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Corneal biomechanics is the intersection at which genetics, microstructure, collagen/matrix homeostasis and repair and related diseases interact with physics to drive curvature change, thus linking these process to refractive function.
Normal corneal structure

Meek et al, IOVS 2005
Boote et al, J Struct Biol 2005
William Bowman, 1847
Morishige et al, JCRS 2007
Winkler et al, IOVS 2013
Spatial corneal property variation

Smolek, IOVS 1990, 1993

Winkler et al, IOVS 2011
The mechanical steady state is *dynamic*.

Dupps & Roberts, 1995, JRS 2001
The biomechanics of keratoconus

What we know:
- Structural abnormalities & loss of interlacing fibrils at Bowman layer (including Morishige 2007)
- Elastic modulus is low (Andreassen 1980)
- The response to an air puff indicates less elastic resistance and other abnormalities (Luce 2005)

Questions of clinical interest:
- What is the relationship between biomechanical properties and topographic features?
- How does this inform our approach to treatments such as collagen crosslinking (CXL)?
- How does corneal geometry influence disease propensity in refractive surgery?
Mechanical-shape associations and hypothesis testing in KC

Sinha Roy & Dupps, IOVS 2011
Experimental computational model of KC progression

Sinha Roy & Dupps, IOVS 2011
Reducing elastic modulus simulates KC progression

Sinha Roy & Dupps, IOVS 2011
3 key observations:
- Thinning was additive to progression but not required
- Steepening was nonlinear as a function of modulus degeneration
- Corneal surface area is minimally changed even at 12D Kmax increase

Sinha Roy & Dupps, IOVS 2011
Steepening driven by elastic weakening

Inflection point is case-specific

$K_{\text{max}} = 47.1 \text{ D}$

Sinha Roy & Dupps, IOVS 2011
Collagenase-mediated tissue model of ectasia

Hong et al, IOVS 2012
Overview of the Crosslinked Cornea

- Caveat: CXL encompasses various approaches
- Common final effect is stromal *stiffening*
  - Increased elastic modulus
  - Decreased rates of enzymatic digestion
  - Reduced corneal permeability
  - Resistance to swelling*
  - Increased autofluorescence
  - Collagen fibril diameter increased 12%*
  - No increase in separation between adjacent collagen molecules
Microstructural Effects of CXL

Hayes et al, PLOS One 2013
Biomechanical Measurement and Characterization of CXL Effect
Ocular Response Analyzer®: a high-speed measure of the corneal bending response
ORA signal and corneal hysteresis (CH)

Luce, JCRS 2005
Custom derived variables

Hallahan et al, Ophth 2014
Does CH increase after crosslinking?

- NO
  - Goldich et al, Cornea 2012
  - Greenstein et al, Cornea 2012
  - Asri et al, JCRS 2011
  - Spoerl et al, JRS 2011
  - Segeghadt et al, JCRS 2010
  - Vinciguerra et al, JRS 2010
  - Goldich et al, Cornea 2009

- 37 custom variables: area under peak 2 increased 35% in KC patients after CXL (Spoerl et al, 2011)
ORA changes with CXL: post-LASIK ectasia

- 31 eyes, before and 3 months after epi-off CXL
- No changes in CH, CRF
  - Peak 1 onset time higher ($p=.002$)
  - Concavity time shorter ($p=.04$)
  - Higher applanation pressures ($p<.004$)

Hallahan et al, ECL 2014
Surface wave elastometry

- Sonic Eye® (PriaVision, Menlo Park CA)
  - Measures time-of-flight of low frequency wave over 4.5 mm distance
  - Elastic modulus related to $\rho V^2$

Dupps et al, JRS 2007
Sonic corneal stiffness interrogation

Wave animation courtesy of Professor Larry Braile, Purdue U
Corneal stiffening and IOP measurement

- 2 human globes
- Intra-vitreal IOP maintained at 30 mmHg
- Crosslinking with glutaraldehyde 4%, 45 min.

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<thead>
<tr>
<th></th>
<th>Before CXL</th>
<th>After CXL</th>
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<tbody>
<tr>
<td>Central Wave Velocity (m/s)</td>
<td>80 ± 3</td>
<td>145 ± 5</td>
</tr>
<tr>
<td></td>
<td>79 ± 4</td>
<td>147 ± 5</td>
</tr>
<tr>
<td>Pneumo (mmHg)</td>
<td>33.5</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>31</td>
<td>79.5</td>
</tr>
<tr>
<td>Tonopen (mmHg)</td>
<td>35</td>
<td>87</td>
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<tr>
<td></td>
<td>36</td>
<td>89</td>
</tr>
</tbody>
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Dupps et al, JRS 2007
3D OCT-based elasticity imaging

Ford et al, J Biomed Opt 2011
OCT elastography: Normal & KC
OCT elastography in human donor globes

Ford et al, JCRS 2014
OCE comparison of CXL effect

Armstrong & Lin et al, JRS 2013
Non-contact *in vivo* Doppler OCE

Shear Modulus = 177kPa
Young’s Modulus = 530kPa

Ford et al, ARVO 2014
Brillouin scattering

Relates to elastic modulus ($M'$): $M' = \rho \lambda^2 \Omega^2 / 4n^2$

Scarcelli et al, IOVS 2013, AJO 2015
Macro-structural Effects of CXL
Corneal collagen crosslinking for KC

- 23 eyes, progression halted, 70% regressed
- UVA/riboflavin, broad pattern approach

Wollensak et al, AJO 2003
Macro-effects of CXL: Computational Modeling Analyses

Geometry

Material properties

FE Mesh

Simulation

Load

Stress/strain/shape & optical solutions

Comparison to actual/desired outcome

Refine surgical algorithm
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